Second Look™ Device Labeling

1 Brief Device Description

Second Look™ is a mammographic computer-aided detection (CAD) system that identifies and highlights potential areas of concern to assist radiologists in breast cancer screening. The CAD algorithms used in the Second Look™ computer system include image processing, feature computations, and pattern recognition technology to detect mammographic features indicative of malignancies. Areas of concern identified include suspicious clusters of microcalcifications, spiculated and non-spiculated masses, architectural distortions, and focal asymmetric densities.

Second Look™ is a self-contained system. The system components include a bar code reader, touch screen monitor, keyboard, digitizer, computer (with dual processors to allow simultaneous digitization and CAD processing), printer, and uninterruptible power supply. The operator loads screening mammography films into the digitizer and enters patient demographic data. The system then digitizes the films, runs the CAD algorithms and creates a printout, or Mammagraph™, for use by the radiologist. The Mammagraph™ contains images of the digitized films with the potential areas of concern clearly marked (see Figure 1).

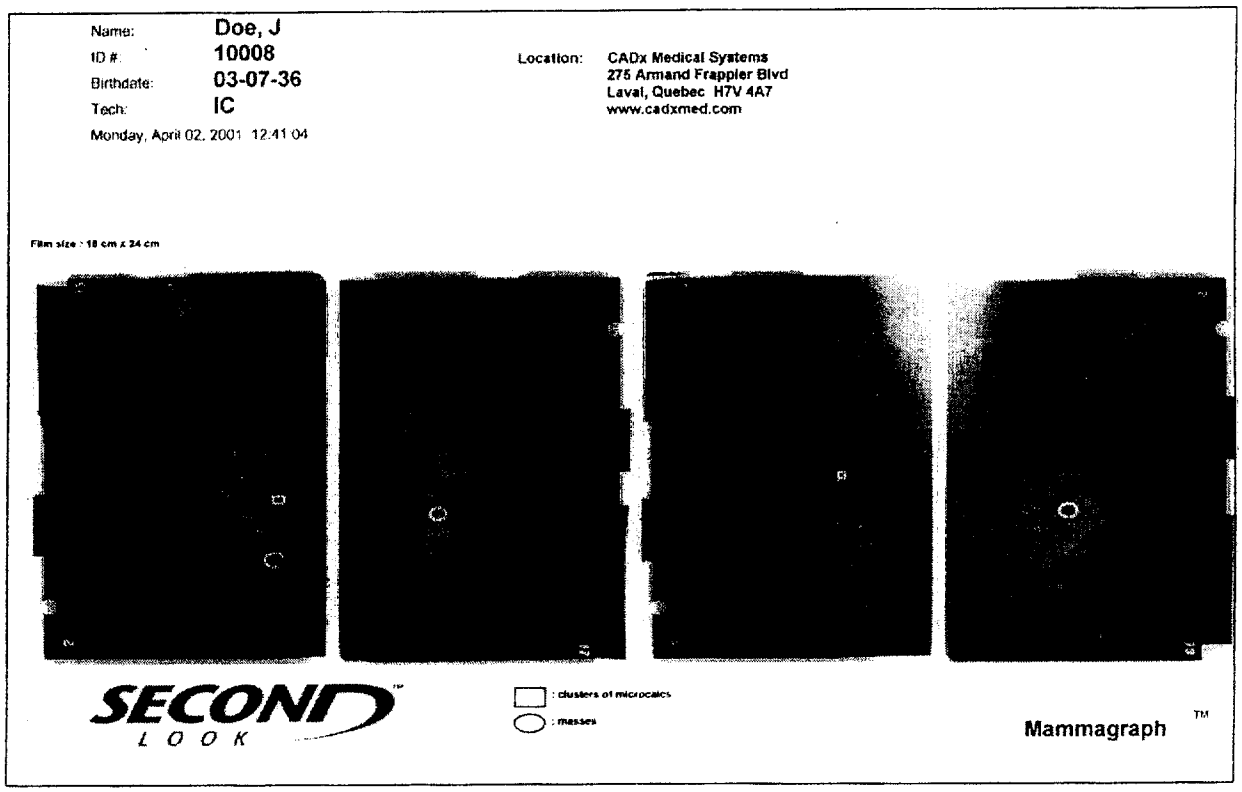


Figure 1: Second Look™ Mammagraph™

Suspicious clusters of microcalcifications are marked on the Mammagraph™ with rectangles (CalcMarks™). Suspicious spiculated and non-spiculated masses, architectural distortions, and focal asymmetric densities are marked on the Mammagraph™ with ellipses (MassMarks™). Each CalcMark™ or MassMark™ is placed at the location of a suspicious lesion detected by Second Look™, with the rectangle or ellipse corresponding to the approximate size of the lesion.

Second Look™ is intended to be used by a radiologist as follows: The radiologist must first review the mammogram in the normal manner and only afterward consult the Mammagraph™ to determine if it has marked any areas of concern that were not observed on the initial review. Second Look™ is designed to put marks on the Mammagraph™ on areas with the mammographic appearance of cancer; however, the vast majority of the marked areas will not contain a malignancy, and it is up to the radiologist to decide, using conventional clinical judgment and reviewing the mammogram itself rather than the Mammagraph™, if the area is suspicious enough to warrant further work-up. Second Look™ is not a diagnostic device, as the Mammagraph™ is intended to be used to assist only in detection and not in interpretation. The system design and its clinical use are compatible with the Mammography Quality Standards Act of 1992 (MQSA).

2 Indications for Use

The Second Look™ computer-aided detection system for mammography is intended to identify and mark regions of interest on standard mammographic views to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

3 Contraindications

There are no contraindications for use of this device.

4 Warnings

Warnings: Radiological Interpretation

- The Second Look™ system assists in breast cancer detection, not interpretation or diagnosis.
- Upon re-evaluation of the films at the locations of CalcMarks™ and MassMarks™, the radiologist uses interpretive skills to determine if the area should be worked-up based on its mammographic appearance.

- **The initial, unassisted film review is critical, because the system will not highlight all areas that the radiologist may detect, and using the system before finishing the unassisted conventional film review runs the risk of inducing a so-called satisfaction-of-search error, in which the radiologist fails to examine the unmarked areas of the films with adequate vigilance.**

    - The system detects approximately 85% of visible cancers, including clustered microcalcifications, spiculated and non-spiculated masses, architectural distortions and focal asymmetric densities. Thus about 15% of visible cancers will not be marked.
    - The system is not designed to highlight interval change between mammographic exams.
    - The system is not designed to highlight asymmetric breast tissue, tubular density/solitary dilated duct, skin thickening, or nipple retraction.

- **The system will highlight many areas that a radiologist determines do not require work-up, on average approximately 1.2 marks per film, or approximately 5.0 marks per 4-view mammogram. Thus, the work-up is determined by the radiologist, and the presence of a mark should not influence the decision that would have been made had the area been noted in the first place.**

    - The radiologist must still use diagnostic skills to differentiate benign from malignant lesions by working-up the area, which may include magnification/compression mammography, ultrasound, or interventional procedures.

- **Therefore, the radiologist's work-up decision should not be altered if the system fails to mark an area that the radiologist has detected on the initial film review and has already decided requires further work-up. Nor should the decision be affected if the system marks an area that the radiologist decides is not suspicious enough to warrant further work-up, whether the area is detected by the radiologist on initial film review or only after being marked by the system.**

Warnings: System Operation

- The system should not be used if it is suspected that any electrical component is defective or inoperable.
- Caution must be exercised to ensure that neckties, jewelry, hair, or loose clothing do not become entangled in moving parts of the system, to prevent the possibility of personal injury or damage to Second Look™.

- Do not place any liquids on or near Second Look™. If a liquid is accidentally spilled on electrical components, immediately shut down the system to prevent any potential electrical shock. Contact your authorized Second Look™ service provider for further instructions.
- Never look into or aim the laser beam at another individual, even if the bar code reader appears to be nonfunctional or turned off. Exposure to laser beam light may result in hazardous laser exposure, which may cause serious injury.
- Ensure that the system is connected to a properly wired and grounded power receptacle. Confirm that the voltage and current requirements are within system specifications to avoid bodily injury from electrical shock or fire hazard.

Warnings: Installation and Maintenance

- Power -- Shut down power to all components prior to cleaning to prevent the possibility of electrical shock.
- Modem Warning -- The modem is to be used by service personnel only in case the system requires remote servicing.
- EMC Warning -- This Second Look™ system has been tested and found to comply with EN 60601-1-2. Compliance with EN 60601-1-2 shows the system is reasonably protected against harmful interference in a typical medical installation. However, this system generates, uses and can radiate radio frequency energy and, if not installed and used in accordance with instructions, may cause or be subject to harmful interference with other devices in the vicinity. If the Second Look™ system appears to cause or be subject to harmful interference, try the following steps to correct the problem:
  - Reorient or relocate the Second Look™ system or the interfering device.
  - Increase the separation between the Second Look™ system and the interfering device.
  - Plug the Second Look™ system into an outlet on a different circuit from the interfering device.
  - Contact your authorized Second Look™ field service provider for further instructions.

- **Uninterruptible Power Supply Warning -- Persons performing troubleshooting or maintenance on the equipment should be aware and cautioned that the Uninterruptible Power Supply (UPS) continues to provide electrical energy during power failures and when disconnected from the main power.**

- Temperature and Humidity Warning -- Second Look system operations must be performed within the following temperature and humidity ranges.
  - Temperature: 60°-90° Fahrenheit (15°-32° Celsius)
  - Humidity: 35-80%

5 Precautions

Precautions: System Operation

- Operator training and review of the Operator's Manual is required prior to using the system.
- The Second Look™ system is protected by an Uninterruptible Power Source (UPS). When the unit beeps constantly for five minutes, stop any operation and shut down the system. The beep indicates that the power source is protecting the equipment after a loss of power.
- To prevent damage to the system, maintain equipment in a well-ventilated, air-conditioned environment.
- Quality Assurance including stepwedge, spatial resolution and file tests, should be performed as per the Operator's Manual.
- Only standard size mammographic films (18 cm x 24 cm or 24 cm x 30 cm) should be used. Films from conventional screen-film mammography should be used. Printed film from full-field digital mammography should not be used.
- Mammography films used in the system should meet MQSA standards.
- Effectiveness and safety in patients with breast implants has not been established for views that include the implant. Only implant-displaced views may be analyzed through the system.
- Effectiveness and safety have not been established for diagnostic views (e.g., magnification/compression views). These views should not be analyzed through the system.
- To prevent film digitization jams, do not use with film labels or tape near the film edge.
- To prevent damage, shut down the system according to the procedures outlined in the Operators Manual.

Precautions: Installation and Maintenance

- This product contains no independently user serviceable parts. To prevent damage to the system, do not attempt to install or repair the Second Look™ system. Only trained personnel are qualified to install or repair the system. For service training, contact CADx Medical Systems Inc. at 1-866-280-CADX (2239).
- Disconnect power cord before moving or servicing.

6 Adverse Effects

The use of Second Look™ adds no known additional risks to screening mammography. There is no direct contact with the patient.

7 Clinical Studies

Two comprehensive studies, ROSE-1 and ROSE-2, were conducted to evaluate the use of the Second Look™ system in breast cancer screening.

ROSE-1

The first, ROSE-1, was a multi-institutional study with 3 components: ROSE-1M assessed the reduction in false negatives resulting from the system's detection of missed cancers; ROSE-1D assessed the sensitivity of the system in detecting cancers on mammograms that led to the diagnosis; and ROSE-1R assessed the reproducibility of the system's markings.

ROSE-1M

The ROSE-1M study assessed the number of previously overlooked cancers that might have been detected and worked up by the radiologist had she or he been using Second Look™. Seventeen (17) institutions enrolled 402 screening mammography cases that were originally interpreted as normal or benign within 24 months prior to the screening mammogram that led to cancer diagnosis. Of these 402 cases 377 had both the current mammogram and the prior mammogram available for analysis. The 377 prior mammograms underwent independent, blinded review by 3 radiologists (the panel) for detection and recommendation of work-up of mammographic abnormalities. At least one of the panel radiologists recommended work-up in 313 cases, with the other 64 cases recommended for work-up by none of them. Of the 313 cases, 177 had one or more work-ups confirmed to be at the locations of subsequently diagnosed cancers by 2 other (truthing) radiologists. The truthing radiologists worked independently of each other but came to consensus over initial disagreements. They worked unblinded, with the help of the subsequent mammogram that led to the diagnosis of cancer.

Of these 177 previously missed cancers, approximately 66% were represented primarily by masses and 34% by microcalcifications. The masses included spiculated and non-spiculated masses, architectural distortions, and asymmetric densities. These 177 mammograms were then processed by Second Look™. The system produced a Mammagraph™ on which MassMarks™ and CalcMarks™ were identified. The locations of these marks were compared to the locations of the subsequently diagnosed cancers. This process measured the sensitivity of the Second Look™ system in detecting missed cancers, but there remained to be determined how many of these would have led the radiologist to recommend work-up.

Since a correct mark by the Second Look™ system in actual clinical practice would only lead to a useful result if the radiologist using it felt that the mark indicated a region that was suspicious enough to warrant further work-up, the number of correct marks needed

to be adjusted downward. As a surrogate method of estimating this adjustment, the proportion of blinded panel radiologists who correctly identified the missed cancers was used as a likelihood multiplier. This proportion was either 0/3, 1/3, 2/3, or 3/3. Use of this proportion resulted in a lower bound to the estimated adjustment, for the following reason. The panel radiologists who failed to identify a region could have failed on the basis of either an error of detection or an error of interpretation, but the distribution of cases between these two types of errors was not recorded. So it was simply assumed that all lesions had been detected by all three of the unaided panelists and that failures to recommend work-up were due strictly to errors of interpretation. Then multiplying by 0/3, 1/3, etc. results in the worst-case scenario for actionability of any lesion marked by the system.

By this method it was determined that of these 177 missed cancer cases 62.7% were marked by the Second Look™, and of these at least 80.3 would have been worked-up if they had been pointed out to the clinical radiologist.

Retrospective review of the 313 cases by the truthing radiologists showed that 242 had retrospectively visible lesions in the location of the subsequent cancer and 71 did not. This 242 included 177 cancers that at least one of the three panel radiologists called actionable plus 65 which none of them called actionable. As a conservative estimate, all 64 of the cases not submitted to the truthing radiologists for determination of lesion visibility were arbitrarily assumed to have retrospectively visible lesions. Using this assumption, the maximum number of retrospectively visible false negative cases is 306 (242 + 64). Therefore, the reduction in false negatives with the use of Second Look™ is at least 26.2% (80.3/306). With a 95% confidence interval of 21.9% to 30.7%, this 26.2% minimum reduction in false negatives is clinically significant.

ROSE-1D

The ROSE-1D study examined the sensitivity of Second Look™ in detecting diagnosed cancers on screening mammograms. Seventeen (17) institutions enrolled 930 subjects with screening mammograms that led to the diagnosis of breast cancer (67% of which were represented primarily by masses and 33% by calcifications). The 930 mammograms were processed by Second Look™. The system correctly marked the cancer in 791 of these 930 cases. Thus, Second Look™ had a sensitivity of 85% for screen-detected cancer cases.

ROSE-1R

The ROSE-1R study evaluated the reproducibility of the Second Look™ system. Twenty-five (25) screen-detected cancer cases from the ROSE-1D study were processed 10 times through each of 3 Second Look™ systems. The system correctly marked the lesion in 745 of 750 cases. Therefore, the Second Look™ system reproducibility was over 99%.

ROSE-2

The second pivotal study, ROSE-2, was a multi-institutional prospective study designed to show that the use of the Second Look™ system did not appreciably increase the number of suspicious regions recommended for further work-up by radiologists reading screening mammograms. The work-up rates of radiologists were prospectively determined before and after the use of Second Look™. In addition, the interpreting radiologists estimated the additional time associated with the use of Second Look™ as a percentage of total reading time.

Ten (10) experienced mammographers at 5 institutions prospectively interpreted a total of 3,946 sequential screening mammograms. Each mammogram was then processed by Second Look™, and the same radiologists then re-evaluated the mammogram with the Mammagraph™. Of the 3,946 cases, 657 were recommended for work-up by radiologists before the use of Second Look™. After the use of Second Look™ an additional 20 cases were recommended for work-up, for a total of 677 cases. Therefore, the work-up rate of radiologists was 16.6% (657 of 3,946) before use of Second Look™ and 17.2 % (677 of 3,946) afterward. The 95% confidence intervals for these work-up rates were (15.5% – 17.8%) before Second Look™ use and (16.0% – 18.4%) with it. This demonstrated that the 0.5% (20 of 3,946) increase in work-up rate due to the use of Second Look™ was statistically and clinically insignificant.

In 3,631 of 3,946 prospective cases (92%) the estimated additional reading time to use Second Look™ was 20% or less.

In addition, historical work-up rates for the same radiologists in the months prior to the prospective cases were compared to their rates before the use of Second Look™ in order to illustrate the variability inherent in the process of reading screening mammograms. For this study, work-up included additional mammographic views, short-interval follow-up, ultrasound, other advanced imaging modalities, or recommendation for biopsy. Of the 3,876 historical cases, 516 were worked-up by radiologists without the use of Second Look™ for a 13.3% historical work-up rate. The 95% confidence interval on this work-up rate was (12.3% – 14.4%). Thus, there was no overlap in the confidence intervals between the historical work-up rate and the work-up rate prior to use of Second Look™ compared to the considerable overlap of confidence intervals between the work-up rates before and after Second Look™ use. Consequently, the inherent variability in radiologist work-up rates was larger than the increase due to the use of Second Look™. This adds further evidence that the increase in work-up rate due to the use of Second Look™ is clinically insignificant.

Conclusions drawn from the studies:

- The use of the Second Look™ system on screening mammograms led to a clinically significant reduction in missed cancers (false negatives) of at least 26.2% (95% CI 21.9%, 30.7%).

- The use of the Second Look™ system led to a clinically and statistically insignificant increase in the number of work-ups recommended by radiologists reading screening mammograms from 16.6% (95% CI 15.5%, 17.8%) unaided to 17.2% % (95% CI 16.0%, 18.4%) aided.

In summary, the Second Look™ system aids a radiologist in detecting breast cancer on screening mammograms.

8 Principles of Operation

Second Look™ uses computer-aided detection (CAD) algorithms to identify suspicious lesions in mammograms. The digitizer creates digital images of mammography films by scanning them into the system, and these CAD algorithms use advanced image processing, feature computations, and pattern recognition technology to analyze the images for potential areas of concern. These potential areas of concern are marked on the Mammagraph™ for use by the radiologist as an additional tool in breast cancer detection.

An overview of the Second Look™ CAD algorithms is shown in Figure 2

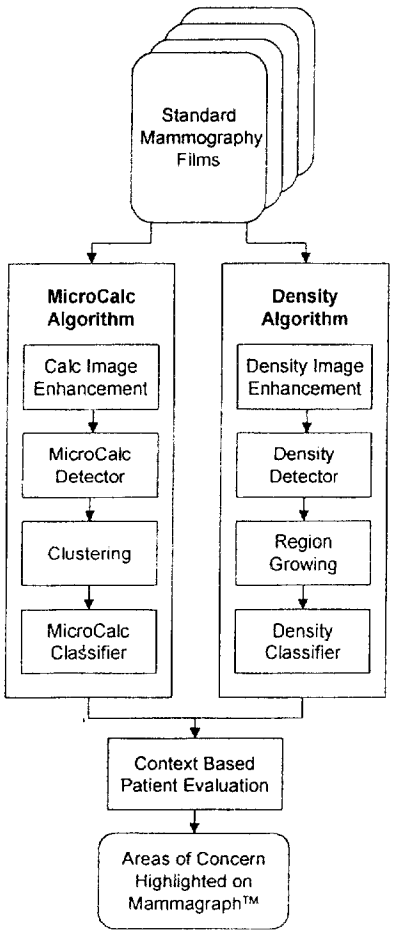
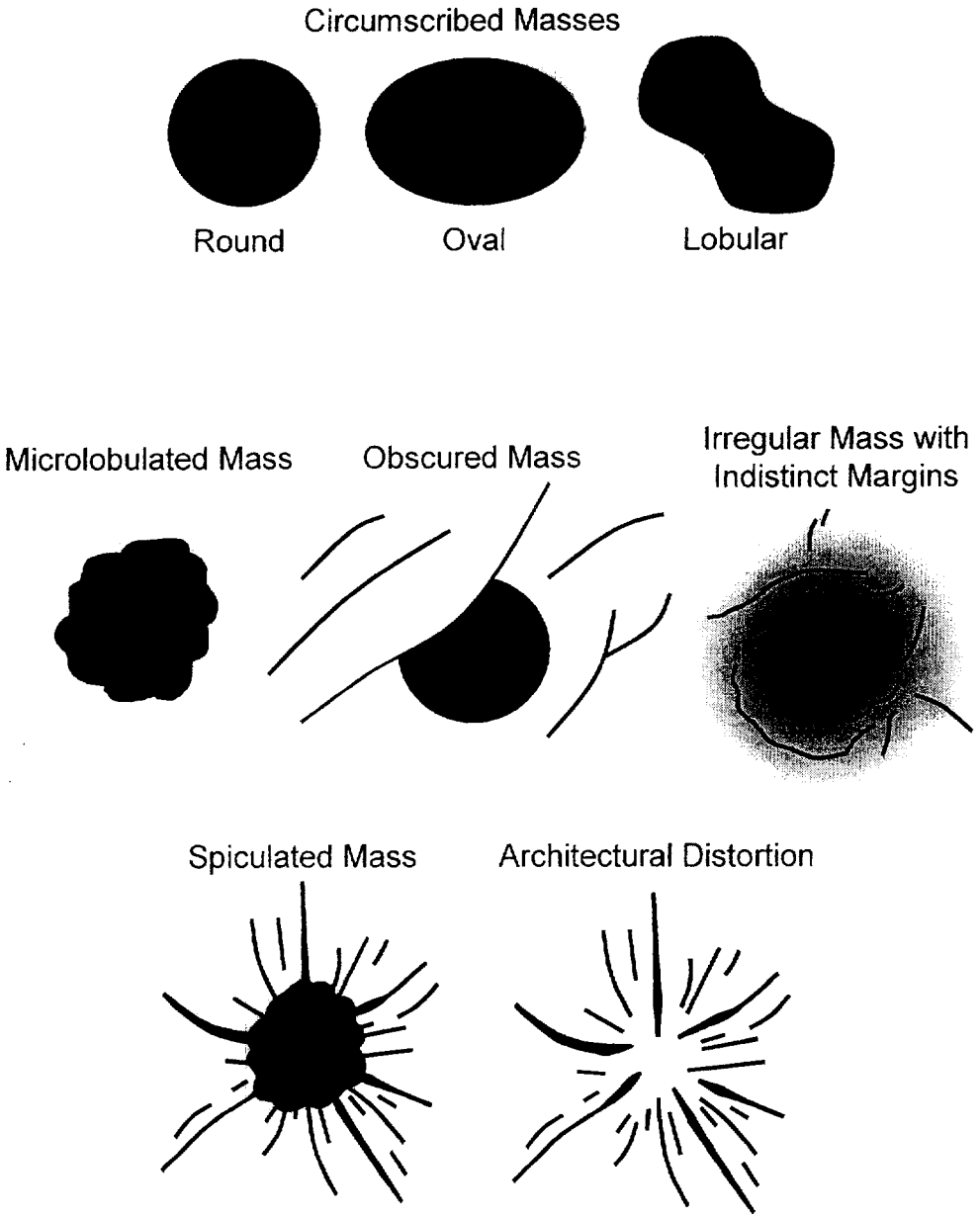


Figure 2: Second Look™ CAD Algorithms Overview

The CAD algorithms begin with image enhancement of the digitized mammographic images to accentuate all areas that could be individual microcalcifications and densities. The microcalcification and density detectors then identify the areas that are most likely to be individual microcalcifications and densities, based on an initial analysis of morphological and intensity measurements. The types of densities detected are

depicted in Figure 3 and include spiculated and non-spiculated masses, architectural distortions, and focal asymmetric densities.



NOTE: Focal asymmetric densities are difficult to depict pictorially, but are detected by Second Look™

Figure 3: Densities Detected by Second Look™

Further analysis of detected areas is accomplished by clustering individual microcalcifications and region growing densities. Clusters include 3 or more individual microcalcifications that are each no more than 3 millimeters apart. Figure 4 depicts portions of three different Mammagraphs™ showing how the system would highlight microcalcification clusters in these examples. Region growing determines the shape of potential densities as shown in Figure 5.

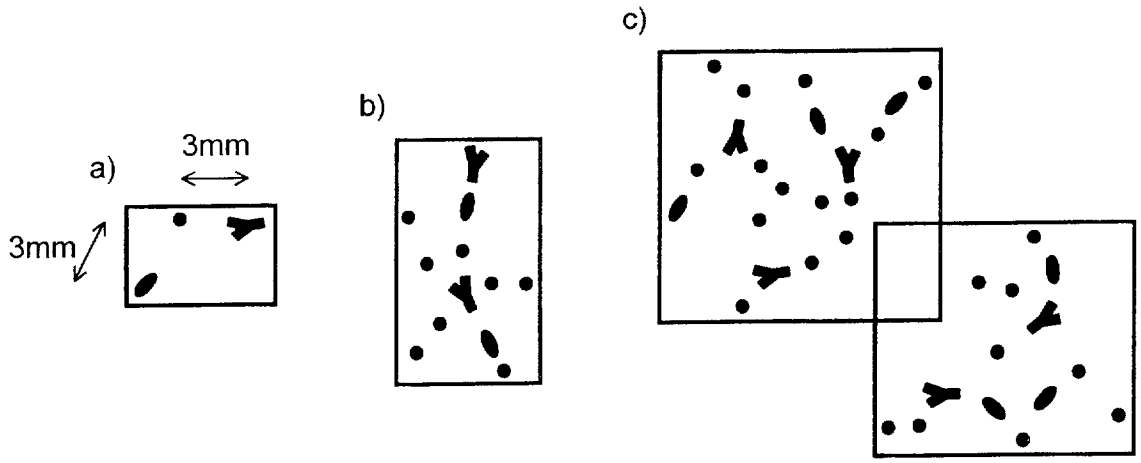


Figure 4: CalcMarks™ Highlighting Microcalcification Clusters with:

a) The minimum number of calcifications
b) The extent of the CalcMark™ enclosing all calcifications considered as part of the cluster
c) Overlapping CalcMarks™ are distinctly highlighted even when clusters are close to each other

After clustering for microcalcification analysis and region growing for density analysis, clinically relevant and mathematical features are then computed to describe each detected cluster of microcalcifications and density. For example, the variability in size and shape of the calcifications in a cluster are good features to describe clusters of microcalcifications. These features are used by microcalcification and density classifiers, which are specifically designed to select the areas most likely to be cancer.

Further analysis uses the context of all areas selected for the patient. For example, each 4-film case can include a total of 3 CalcMarks™ and 6 MassMarks™, with no more than 2 CalcMarks™ and 3 MassMarks™ in any film. Simultaneous analysis of all areas of concern detected in the patient allows the locations most likely to be cancer to be highlighted on the Mammagraph™.

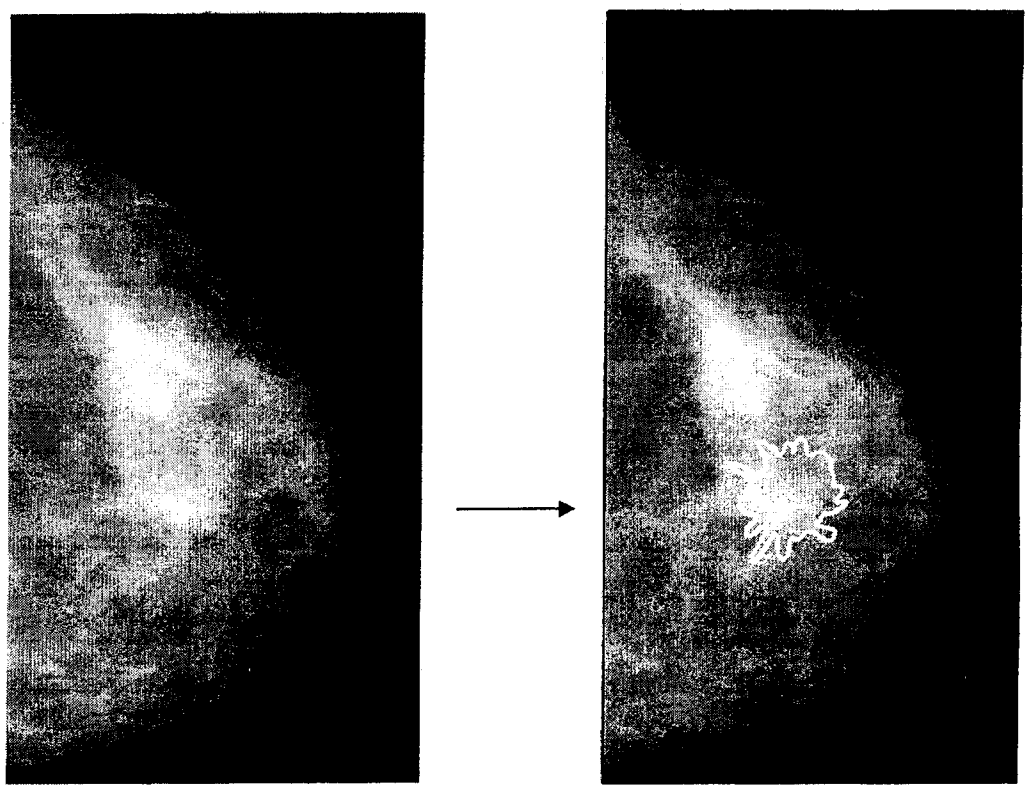


Figure 5: Region Growing to Determine Shape of Density

9 Conformance to Standards

Second Look™ complies with the following Electrical Safety and Electromagnetic Compatibility (EMC) Standards:

Electromagnetic Emissions:

- EMC Directive 89 /336/EEC
- Medical Directive 93/42/EEC
- EN55011/1991 Class A
- CISPR 11/1190

Electromagnetic Immunity:

- EMC Directive 89/336/EEC
- Medical Directive 93/42/EEC
- EN60601-1-2/1993 Part 1 & 2

Medical Electrical Safety:

- IEC/EN 60601-1/1995 Amendment A1 & A2

- This system provides CLASS I protection from electrical shock as defined by EN 60601-1
- UL 2601-1, Second Edition
- CAN/CSA C22.2 No. 601.1-M90

Second Look™ has also been tested and found to be Y2K compliant.

10 How Supplied

The Second Look™ system includes the following components:

- Touch Screen Monitor
- Bar Code Reader
- Digitizer
- Uninterruptible Power Supply
- Computer
- Printer
- Keyboard

11 Manuals

Three manuals are distributed with the Second Look™ system:

- Second Look™ Operator's Manual – describes proper operation and maintenance of the system
- Second Look™ Quick Reference Guide – a quick summary of the Operator's Manual
- Second Look™ Radiologist Training Manual – provides guidance for use of the Mammagraph™

12 References

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3 Harvey JA, Fajardo LL, Innis CA. "Previous Mammograms in Patients with Impalpable Breast Carcinoma: Retrospective vs. Blinded Interpretation." *AJR*, 161, pp. 1167-1172, 1993.

4 Martin JE, Moskowitz M, Milbrath JR. "Breast Cancer Missed by Mammography." *AJR*, 132, pp. 737-739, 1979.

5 Schmidt RA, Nishikawa RM. "Digital Screening Mammography." *PPO Updates*, 8:7, pp. 1-16, 1994.

6 Thurfjell EL, Lernevall KA, Taube AAS. "Benefit of Independent Double Reading in a Population-based Mammography Screening Program." *Radiology*, 191, pp. 241-244, 1994.

7 Economic Impact Analysis of Regulations Under the Mammography Quality Standards Act of 1992, U.S. Food and Drug Administration and Eastern Research Group, Inc., Task Order No.1, Contract No. 223-94-8031, October 7, 1997.

8 Quality Determinants of Mammography, Clinical Practice Guideline Number 13, Agency for Health Care Policy and Research Publication No. 95-0632: October, 1994.